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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 08/487,623
Filing Date: June 7, 1995
Appellant(s): LOVGREN

Ronald J. Kubovcik, Reg. No. 25,401
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed December 8, 1997 and the Supplemental appeal brief filed August 17, 1998.

(1) Real Party in Interest

The brief does not contain a statement identifying the Real Party in Interest. Therefore, it is presumed that the party named in the caption of the brief is the Real Party in Interest, i.e., the owner at the time the brief was filed. The Board, however, may exercise its discretion to require an explicit statement as to the Real Party in Interest.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is is described in the sentence bridging pages 2-3, "The invention is the discovery that by appropriate control of the amount of microparticles and the amount of sample, the concentration of an analyte in a predetermined, clinically relevant range of analyte can be determined by measurement of the signal from a surace of a single microparticle. The amount of microparticles and amount of sample are determined by experimentation using samples having a known concentration of analyte."

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

The rejection of claims 6, 7, 10, 13, and 16-18 stand or fall together because appellant's brief does not include a statement that this grouping of claims does not stand or fall together and reasons in support thereof. See 37 CFR 1.192(c)(7).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

5,028,545	SOINI	7-1991
5,089,391	BUECHLER et al	2-1992

Ekins, R.P., and F.W. Chu. "Multianalyte Microspot Immunoassay -- Microanalytical "Compact Disk" of the Future." Clinical Chemistry, Vol. 37, No. 11 (1991), pp. 1955-1967.

Bush, C.E., L.J. Di Michele, W.R. Peterson, D.G. Sherman, and J.H. Godse. "Solid-Phase Time-Resolved Fluorescence Detection of Human Immunodeficiency Virus Polymerase Chain Reaction Amplification Products." Analytical Biochemistry, Vol. 202 (1992), pp. 146-151.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 6, 7, 10, 13, and 16-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 13 is unclear as to what criteria are used to "predetermine" the amount of microparticles and sample so as to correlate measurement of a single microparticle to analyte concentration, i.e., how does the "predetermined" amount of microparticles and sample volume of the improvement step differ from the microparticle and sample volumes of the preamble in the Jepson claim. Measurement analyte concentration from the signal measured from a single microparticle implies a critical relationship between the amount of sample analyte concentration expected in a predetermined volume of sample and the amount of affinity microparticles used. Critical limitations should be positively stated not merely implied.

Claims 6, 7, 10, 13, and 16-18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

It is unclear how the claimed invention differs from routine optimization in determining a "predetermined" amount of affinity microparticles and sample volume which would not spread the bottom end of analyte concentration over so large a surface area as to render bound analyte-specific label indistinct from non-specific backgraound label binding.

Claims 6, 10, 13, and 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Soini et al (U.S. Pat. No. 5,028,545) in view of Ekins et al (*Clinical Chemistry*, 37(11):1955-1967, 1991).

Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over the references as applied to claim 13 above, and further in view of Bush et al (*Analytical Biochemistry*, 202:146-151, 1992).

Soini et al describes high detection sensitivity biospecific assay methods using time-resolved fluorescent tracers and microparticles coated with analyte specific bioaffinity reactants using flow cytometry and microfluorometric measurement systems (col. 1, lines 27-56; col. 2, lines 20-37). Soini et al differs in failing to disclose explicitly, basic concepts used to optimize biospecific assay methods, e.g., the interrelationship between sample analyte and assay reactants used to provide maximal sensitivity as instantly claimed such that concentraion of an analyte in a predetermined, clinically relevant range of analyte can be determined by measurement of signal from a surface of a single microparticle.

Ekins et al teaches that all immunoassays rely on the measurement of antibody (i.e., bioaffinity reactant A) occupancy by analyte. Ekins et al further teaches that if the amount of antibody is vanishingly small, fractional antibody occupancy is independent of both the amount of antibody concentration and sample volume. While Ekins et al exemplifies adjustment of antibody concentration and sample, i.e., analyte, concentration to optimize a microspot immunoassay, Ekins et al explicitly comments on the generic applicability of the teachings therein (see the entire article).

Bush et al is added to show the applicability of time-resolved fluorescent labelled microparticle based assays to hybridization formats.

Therefore, minus a showing of unexpected results, it would have been obvious to combine the generic optimization procedure of Ekins et al school in any given biospecific assay method, such as the fluorescent labelled microparticle based assay of Soini et al

or Bush et al, in order to obtain maximum sensitivity and/or minimize random errors as suggested by Ekins et al. In addition, one of ordinary skill in the art would have considered at least the following factors in optimizing a given biospecific assay: the expense of bioaffinity reagents, the clinically (or otherwise) significant result range, the type of sample being asssayed, the specificity and affinity of the bioaffinity reagent for analyte, the desired time to result, etc.

(11) Response to Argument

Claims 6, 7, 10, 13, and 16-18 rejected under 35 U.S.C. 112, second paragraph.

Appellants, in Appeal Brief, argue that their invention is the discovery that the analyte concentration is a sample can be measured from the surface of a single microparticle by adjusting the relative amounts of microparticles and sample.

In the Supplemental Appeal Brief, appellants argue that the examiner's statement that the criteria used to "predetermine" the amount of microparticles and sample so as to correlate measurement of a single microparticle to analyte concentration has no meaning and is not a proper basis for rejecting the claims under 35 U.S.C. 112, second paragraph. Claim 13 precisely recites that "predetermined" amounts are amounts determined by any means enabling a person of ordinary skill in the art to determine an individual microparticle emitting signal strength which corresponds to the analyte concentration in the sample. Thus, a person of ordinary skill in the art can readily determine whether the amount of sample and the number of microparticles used in a biospecific assay method as recited in the claims is such that each individual

microparticle emits a signal strength that corresponds to the analyte concentration in a sample.

Claim 13 recites: "contacting a predetermined amount of said sample, a predetermined number of uniformly sized microparticles coaated with said bioaffinity reactant A and said labelled bioaffinity reactant B labelled with a luminescent label such that, after the specific binding of the analyte in the sample to said predetermined number of uniformly sized microparticles, each individual microparticle emits a signal strength that corresponds to the analyte concentration in the sample, and measuring the signal strength from an individual microparticle using a measuring means capable of reading the luminescence from an individual microparticle, and determining the analyte concentration in the sample by comparing said signal strength measured from said individual microparticle with a standardization curve, wherein said standardization curve is a mean of the signal strength of said predetermined number of uniformly sized microparticles."

Thus, there is no recitation nor guidance in the claims which correspond to appellants' arguments, i.e., a means of "predetermining" microparticle and sample amounts. The term remains unclear and indefinite concerning how one "predetermines" the proper amounts of microparticle and sample so that each individual microparticle emits a signal strength that corresponds to the analyte concentration in the sample.

Claims 6, 7, 10, 13, and 16-18 under 35 U.S.C. 112, first paragraph.

Appellants argue that the specification includes various methods for measurement of individual microparticles and discuss procedures of these various methods. Appellants argue that the examiner has not explaned why determining

analyte concentration based upon individual microparticle signal would require undue, or excessive, experimentation.

The issue is NOT whether one of ordinary skill in the art would be able to measure an individual microparticle as of January 18, 1994. It is admitted that individual microperticles or "cells" can be measured by techniques such as flow cytometry, CCD microscopy, etc. The issue is how the instant "predetermination" of affinity microparticles and sample differs from routine optimization. In paper no. 9, December 10, 1996, applicants argued this is NOT optimization because the skilled artisan would NOT optimize by DECREASING the amount of microparticles being used. Rather, the skilled artisan would INCREASE the binding surface when small amounts of analytes were to be mesured. There is no evidence of record to indicate that this is the state of the art *per se*. It is respectfully submitted that multiple considerations are being balanced to optimize an assay. It is further submitted that it is generally accepted in the art that increasing the available binding surface area will increase the probability of analyte reacting with its binder and therefore decrease the overall assay time. However, such an increased surface area also increase the area over which diffential signal is spread. A factor that the skilled artisan would have also been aware of and would have considered in optimizing the assay parameters.

Therefore, because appellants argue that "predetermination" is not mere optimization, the subject matter of the instant claims doe not appear to be described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 6, 7, 10, 13, and 16-18 rejected under 35 U.S.C. 103(a).

Appellants argue that the examiner has misinterpreted the prior art references in an effort to reconstruct appellants' invention based on hindsight analysis in light of appellants' disclosure.

The examiner has considered appellants' argument, but does not find it persuasive because it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443, F.2d 1392, 170 USPQ 209 (CCPA 1971).

Appellants argue that the examiner has failed to cite any art that discloses or suggests that analyte concentration of a sample can be measured from inidividual microparticles.

The examiner's interpretation of Soini et al, col. 2, lines 20-37 is wrong. A proper interpretation is critical to the resolution of the 103 issue. The primary issue relates to the interpretation of the sentence: "A sufficient number of microspheres are analyzed and the fluorescence signals from each microsphere are registered in a computer."

The examiner has considered appellants' arguments, but does not find them persuasive. Soini et al explicitly recites "measuring the concentration of analyte on each microsphere" on the basis of bound label (col. 1, lines 53-55). Soini et al explicitly teaches incubating sample, microspheres and labelled reactants "in smallest possible

volume" to achieve a complete reaction in a short time (col. Lines 20-25). Soine et al discusses analyzing a sufficient number of microspheres, but does not discuss what number of microspheres are initially chosen for reaction, i.e., how to predetermine the amount of microspheres and sample used in the smallest possible volume.

Appellants do not understand how Ekins et al can be applied in combination with Soini et al when the authors admit that the definitions of sensitivity and precision are in dispute. Appellants argue that the reference can only be read in terms of the fractional occupancy concept and that the teaching of the reference must include Fig. 8 and explanations at pages 1961 and 1962. Appellants' invention is totally unrelated to the principle of fractional occupancy.

The examiner has considered appellants' argument, but does not find it persuasive. Ekins et al teach a microspot which is analogous to the instant microparticle and the microdisc is analogous to the instant predetermined number of microparticles.

Appellants argue that while Bush et al teach the use of time-resolved fluorescence as a method for detecting an immobilized nucleic acid, the reference does not teach optimization of the quantification of the claimed methodology.

As stated in the rejection, Bush et al is added to show the applicability of time-resolved fluorescent labelled microparticle based assays to hybridization formats.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

RODNEY P SWARTZ, PH.D
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